

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
26 June 2003 (26.06.2003)

PCT

(10) International Publication Number  
**WO 03/051851 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 241/24**,  
A61K 31/495, A61P 25/18

S-431 83 (SE). **GREASLEY, Peter** [GB/SE]; Molndal, S-431 83 (SE). **TERRICABRA, Emma** [SE/SE]; Molndal, S-431 83 (SE). **WILSTERMANN, Johan, Michael** [SE/SE]; Molndal, S-431 83 (SE).

(21) International Application Number: PCT/GB02/05742

(22) International Filing Date:  
18 December 2002 (18.12.2002)

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0104330-6 19 December 2001 (19.12.2001) SE

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(71) Applicant (*for all designated States except MG, US*): **ASTRAZENECA AB** [SE/SE]; Sodertalje, S-151 85 (SE).

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for MG only*): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

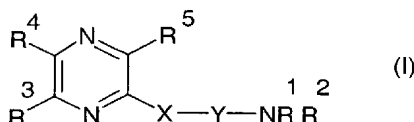
(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BERGGREN, Anna, Ingrid, Kristina** [SE/SE]; Molndal, S-431 83 (SE). **BOSTROM, Stig, Jonas** [SE/SE]; Molndal, S-431 83 (SE). **ELEBRING, Stig, Thomas** [SE/SE]; Molndal,

**Published:**  
— with international search report

[Continued on next page]

(54) Title: 5, 6-DIARYL-PYRAZINE-2-AMIDE DERIVATIVES AS CB1 ANTAGONISTS



(57) Abstract: The present invention relates to compounds of formula (I), and pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, in which R<sup>1</sup> and R<sup>2</sup> independently represent: a C<sub>1-6</sub>alkyl group; an optionally substituted (amino)C<sub>1-4</sub>alkyl- group; an optionally substituted non-aromatic C<sub>3-15</sub>carbocyclic group; a (C<sub>3-12</sub>cycloalkyl)C<sub>1-3</sub>alkyl- group; a group -(CH<sub>2</sub>)<sub>r</sub>(phenyl)<sub>s</sub> in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by Z; naphthyl; anthracenyl; an optionally substituted saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; 1-adamantylmethyl; a group - (CH<sub>2</sub>)<sub>t</sub> Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted and Het represents an optionally substituted aromatic heterocycle; or R<sup>1</sup> represents H and R<sup>2</sup> is as defined above; or R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom to which they are attached represent a saturated optionally substituted 5 to 8 membered heterocyclic group as defined above; X is CO or SO<sub>2</sub>; Y is absent or represents NH optionally substituted by a C<sub>1-3</sub>alkyl group; R<sup>3</sup> and R<sup>4</sup> independently represent phenyl, thienyl or pyridyl substituted by Z; Z represents a C<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di C<sub>1-3</sub>alkylamino, mono or di C<sub>1-3</sub>alkylamido, C<sub>1-3</sub>alkylsulphonyl, C<sub>1-3</sub>alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C<sub>1-3</sub>alkyl carbamoyl, sulphonyl and acetyl; and R<sup>5</sup> is H, a C<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkoxymethyl group, trifluoromethyl, a hydroxyC<sub>1-3</sub>alkyl group, C<sub>1-3</sub>alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C<sub>1-3</sub>alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula -CONHNH<sup>a</sup>R<sup>b</sup>, with the provisos; and processes for preparing such compounds, their use in the treatment of obesity, psychiatric and neurological disorders, to methods for their therapeutic use and to pharmaceutical compositions containing them.

WO 03/051851 A1



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## 5, 6-DIARYL-PYRAZINE-2-AMIDE DERIVATIVES AS CBI ANTAGONISTS

### Field of invention

5 The present invention relates to certain pyrazine carboxamide compounds of formula I, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, to methods for their therapeutic use and to pharmaceutical compositions containing them.

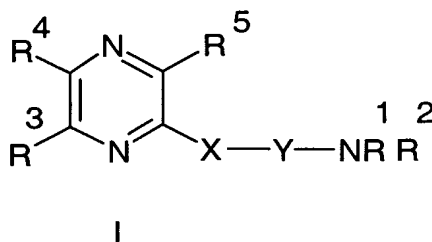
### 10 Background of the invention

It is known that certain CB<sub>1</sub> modulators (known as antagonists or inverse agonists) are useful in the treatment of obesity, psychiatric and neurological disorders (WO01/70700 and EP 656354). However, there is a need for CB<sub>1</sub> modulators with improved  
15 physicochemical properties and/or DMPK properties and/or pharmacodynamic properties.

Pyrazinecarboxamides are reported to possess antithrombotic properties (WO 92/ 02513). The compounds disclosed in this document are disclaimed from the compound claims of the present invention. 5,6-Diphenyl-2-pyrazinecarboxylic acid is disclosed in CH 458 361.  
20

### Description of the invention

The invention relates to compounds of the general formula (I)  
25



and pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, in which

$R^1$  and  $R^2$  independently represent :

a  $C_{1-6}$ alkyl group;

5 an (amino) $C_{1-4}$ alkyl- group in which the amino is optionally substituted by one or more  $C_{1-3}$ alkyl groups;

an optionally substituted non-aromatic  $C_{3-15}$ carbocyclic group;

a ( $C_{3-12}$ cycloalkyl) $C_{1-3}$ alkyl- group;

a group  $-(CH_2)_r(phenyl)_s$  in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2

10 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally

15 one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more  $C_{1-3}$ alkyl groups, hydroxy or benzyl ;

1-adamantylmethyl;

a group  $-(CH_2)_t$  Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more  $C_{1-3}$ alkyl groups and Het represents an aromatic heterocycle

20 optionally substituted by one, two or three groups selected from a  $C_{1-5}$ alkyl group, a  $C_{1-5}$ alkoxy group or halo;

or  $R^1$  represents H and  $R^2$  is as defined above;

or  $R^1$  and  $R^2$  together with the nitrogen atom to which they are attached represent a

saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one

25 of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more  $C_{1-3}$ alkyl groups, hydroxy or benzyl ;

X is CO or SO<sub>2</sub>;

30 Y is absent or represents NH optionally substituted by a  $C_{1-3}$ alkyl group;

$R^3$  and  $R^4$  independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one, two or three groups represented by Z;

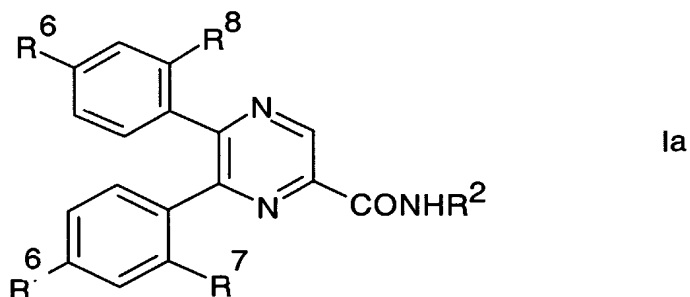
- 5 Z represents a  $C_{1-3}$ alkyl group, a  $C_{1-3}$ alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di  $C_{1-3}$ alkylamino, mono or di  $C_{1-3}$ alkylamido,  $C_{1-3}$ alkylsulphonyl,  $C_{1-3}$ alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di  $C_{1-3}$ alkyl carbamoyl, sulphamoyl and acetyl; and
- 10  $R^5$  is H, a  $C_{1-3}$ alkyl group, a  $C_{1-3}$ alkoxymethyl group, trifluoromethyl, a hydroxy $C_{1-3}$ alkyl group,  $C_{1-3}$ alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di  $C_{1-3}$ alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula  $-\text{CONHNR}^a\text{R}^b$  wherein  $R^a$  and  $R^b$  are as previously defined for  $R^1$  and  $R^2$  respectively;
- 15 with the proviso that when  $R^1$  and  $R^2$  together with the nitrogen atom to which they are attached represent 4-methylpiperazin-1-yl or  $R^1$  represents H and  $R^2$  represents methyl or 1-benzylpiperidin-4-yl; X is CO; Y is absent and  $R^5$  is H; then  $R^3$  and  $R^4$  do not both represent 4-methoxyphenyl.
- 20 Further values of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  in compounds of formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

25 In one group of compounds of formula I,  $R^1$  represents H,  $R^2$  represents cyclohexyl, X is CO and Y is absent.

In a second group of compounds of formula I,  $R^1$  and  $R^2$  together with the nitrogen atom to which they are attached represent 1-piperidinyl.

30 In a third group of compounds of formula I,  $R^1$  represents H and  $R^2$  represents phenyl.

A fourth group of compounds of formula I is represented by formula Ia



5 and pharmaceutically acceptable salts, solvates and crystalline forms thereof, in which

$R^2$  represents cyclohexyl, 1-piperidinyl or phenyl ;

$R^6$  represents H, chloro, bromo, methyl or methoxy; and

when  $R^7$  represents H,  $R^8$  represents H or chloro; and

when  $R^7$  represents chloro,  $R^8$  represents H or chloro.

10

In a fifth group of compounds of formula I  $R^5$  is H.

In a sixth group of compounds of formula I X is CO.

15

In a seventh group of compounds of formula I X is  $SO_2$ .

In an eighth group of compounds of formula I Y is absent.

“Pharmaceutically acceptable salt”, where such salts are possible, includes both

20

pharmaceutically acceptable acid and base addition salts. A suitable pharmaceutically

acceptable salt of a compound of Formula I is, for example, an acid-addition salt of a

compound of Formula I which is sufficiently basic, for example an acid-addition salt with  
an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic,

citric or maleic acid; or, for example a salt of a compound of Formula I which is

25

sufficiently acidic, for example an alkali or alkaline earth metal salt such as a sodium,

calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

5 Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates. Isomers may be separated using conventional techniques, e.g.  
10 chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not  
15 cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention. All tautomers, where possible, are included within the scope of the invention.

The following definitions shall apply throughout the specification and the appended  
20 claims.

Unless otherwise stated or indicated, the term "alkyl" denotes either a straight or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl and t-butyl. Preferred alkyl groups are methyl, ethyl, propyl,  
25 isopropyl and tertiary butyl.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

30 Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine, bromine or iodine.

Specific compounds of the invention are one or more of the following:

*N*-(1-piperidinyl)-5,6-diphenyl-2-pyrazinecarboxamide;

*N*-(1-piperidinyl)-5,6-bis(4-bromophenyl)-2-pyrazinecarboxamide;

*N*-(1-piperidinyl)-5,6-bis(4-methylphenyl)-2-pyrazinecarboxamide;

5 *N*-(1-piperidinyl)-5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxamide;

*N*-(1-piperidinyl)-5,6-bis(4-chlorophenyl)-2-pyrazinecarboxamide;

*N*-(1-piperidinyl)-5,6-bis(2-chlorophenyl)-2-pyrazinecarboxamide;

*N*-cyclohexyl-5,6-diphenyl-2-pyrazinecarboxamide;

*N*-cyclohexyl-5,6-bis(4-bromophenyl)-2-pyrazinecarboxamide;

10 *N*-cyclohexyl-5,6-bis(4-methylphenyl)-2-pyrazinecarboxamide;

*N*-cyclohexyl-5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxamide;

*N*-cyclohexyl-5,6-bis(4-chlorophenyl)-2-pyrazinecarboxamide;

*N*-cyclohexyl-5,6-bis(2-chlorophenyl)-2-pyrazinecarboxamide;

*N*,5,6-triphenyl-2-pyrazinecarboxamide;

15 *N*-phenyl-5,6-bis(4-methylphenyl)-2-pyrazinecarboxamide;

*N*-phenyl-5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxamide;

*N*-phenyl-5,6-bis(4-chlorophenyl)-2-pyrazinecarboxamide;

*N*-phenyl-5,6-bis(2-chlorophenyl)-2-pyrazinecarboxamide;

*N*-(1-piperidinyl)-5-(4-chlorophenyl)-6-(2,4-dichlorophenyl)-2-pyrazinecarboxamide; and

20 *N*-(1-piperidinyl)-6-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-pyrazinecarboxamide;

and where applicable, optical isomers, tautomers, stereoisomers and racemates thereof as well as pharmaceutically acceptable salts, solvates and crystalline forms thereof.

#### Methods of preparation

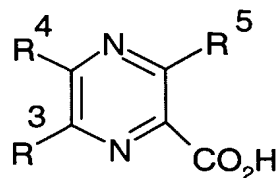
25

The compounds of the invention may be prepared as outlined below according to any of the following methods. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

30

Compounds of formula I in which X is CO may be prepared by reacting a compound of formula II





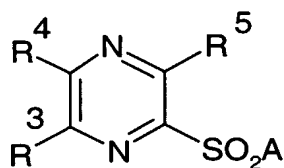
II

in which  $R^3$ ,  $R^4$  and  $R^5$  are as previously defined with an amine of formula III



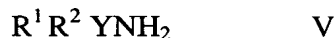
in an inert solvent, for example dichloromethane, in the presence of a coupling agent, for example a carbodiimide, eg 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, and optionally in the presence of a catalyst, for example a basic catalyst, eg 4-dimethylamino-  
10 pyridine, at a temperature in the range of  $-25^\circ\text{C}$  to  $150^\circ\text{C}$ .

Compounds of formula I in which X is  $\text{SO}_2$  may be prepared by reacting a compound of formula IV



IV

15 in which  $R^3$ ,  $R^4$  and  $R^5$  are as previously defined and A represents halo with an amine of formula IV



20 in an inert solvent, for example dichloromethane, and optionally in the presence of a catalyst, for example a basic catalyst, eg 4-dimethylamino-pyridine, at a temperature in the range of  $-25^\circ\text{C}$  to  $150^\circ\text{C}$ .

Compounds of formulae II, III, IV and V may be prepared as described in the Examples and by other methods known to those skilled in the art. Certain compounds of formulae II, III, IV and V are novel and are claimed as a further aspect of the present invention as  
5 useful intermediates. Specifically claimed are compounds of formula II in which  $R^3$ ,  $R^4$  and  $R^5$  are as previously defined with the exception of 5,6-diphenyl-2-pyrazinecarboxylic acid and 5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxylic acid.

The compounds of the invention may be isolated from their reaction mixtures using  
10 conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual  
15 reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

The expression "inert solvent" refers to a solvent which does not react with the starting  
20 materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

#### Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal,  
25 vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient or a pharmaceutically acceptable addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated  
5 by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

A compound of the invention may also be combined with other anti-obesity agents such as  
10 Orlistat or a monoamine reuptake inhibitor, for example Sibutramine. Furthermore, a compound of the invention may also be combined with therapeutic agents that are useful in the treatment of disorders or conditions associated with obesity (such as type II diabetes, metabolic syndrome, dyslipidemia, impaired glucose tolerance, hypertension, coronary heart disease, non-alcoholic steatorrheic hepatitis, osteoarthritis and some cancers) and  
15 psychiatric and neurological conditions.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants,  
20 diluents and/or carriers.

#### Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders  
25 such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders(e.g. Multiple Sclerosis), Raynaud's syndrome, Parkinson's disease, Huntington's chorea and  
30 Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, septic shock and diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea). The compounds are

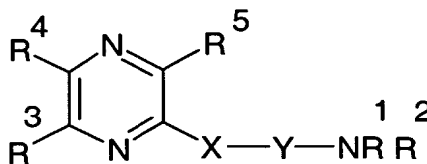
also potentially useful as agents in treatment of extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms. The compounds may also eliminate the increase in weight which normally accompanies the  
5 cessation of smoking.

In another aspect the present invention provides a compound of formula I as previously defined for use as a medicament.

10 In a further aspect the present invention provides the use of a compound of formula I (including the compounds of the proviso) in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention  
15 disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g.  
20 treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders such as schizophrenia and bipolar  
25 disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders,  
30 septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine,

opiates, etc) withdrawal symptoms comprising administering a pharmacologically effective amount of a compound of formula I



I

and pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, in which

$\text{R}^1$  and  $\text{R}^2$  independently represent :

a  $\text{C}_{1-6}$ alkyl group;

an (amino) $\text{C}_{1-4}$ alkyl- group in which the amino is optionally substituted by one or more

$\text{C}_{1-3}$ alkyl groups;

an optionally substituted non-aromatic  $\text{C}_{3-15}$ carbocyclic group;

a ( $\text{C}_{3-12}$ cycloalkyl) $\text{C}_{1-3}$ alkyl- group;

a group  $-(\text{CH}_2)_r(\text{phenyl})_s$  in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups

represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more  $\text{C}_{1-3}$ alkyl groups, hydroxy or benzyl ;

1-adamantylmethyl;

a group  $-(\text{CH}_2)_t \text{Het}$  in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more  $\text{C}_{1-3}$ alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a  $\text{C}_{1-5}$ alkyl group, a  $\text{C}_{1-5}$ alkoxy group or halo;

or  $\text{R}^1$  represents H and  $\text{R}^2$  is as defined above;

or  $R^1$  and  $R^2$  together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more  $C_{1-3}$ alkyl groups, hydroxy or benzyl ;

5

X is CO or  $SO_2$  ;

Y is absent or represents NH optionally substituted by a  $C_{1-3}$ alkyl group;

10  $R^3$  and  $R^4$  independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one , two or three groups represented by Z;

Z represents a  $C_{1-3}$ alkyl group, a  $C_{1-3}$ alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di  
15  $C_{1-3}$ alkylamino, mono or di  $C_{1-3}$ alkylamido,  $C_{1-3}$ alkylsulphonyl,  $C_{1-3}$ alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di  $C_{1-3}$ alkyl carbamoyl, sulphamoyl and acetyl; and

$R^5$  is H, a  $C_{1-3}$ alkyl group, a  $C_{1-3}$ alkoxymethyl group, trifluoromethyl, a hydroxy $C_{1-3}$ alkyl group,  $C_{1-3}$ alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di  $C_{1-3}$ alkylcarbamoyl,  
20 acetyl, or hydrazinocarbonyl of formula  $-CONHNR^aR^b$  wherein  $R^a$  and  $R^b$  are as previously defined for  $R^1$  and  $R^2$  respectively;

to a patient in need thereof.

25 The compounds of the present invention are particularly suitable for the treatment of obesity, e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound.

ExamplesAbbreviations

DCM - dichloromethane

5 DMF - dimethylformamide

DMAP - 4-dimethylaminopyridine

EDC - 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

TEA – triethylamine

TFA – trifluoroacetic acid

10 DMSO-dimethyl sulfoxide

DEA - Diethylamine

PCC - Pyridinium chlorochromate

DCM - Dichloromethane

15 t triplet

s singlet

d doublet

q quartet

qvint quintet

20 m multiplet

br broad

bs broad singlet

dm doublet of multiplet

bt broad triplet

25 dd doublet of doublet

General Experimental Procedures

Mass spectra were recorded on either a Micromass ZQ single quadrupole or a Micromass LCZ single quadrupole mass spectrometer both equipped with a pneumatically assisted electrospray interface (LC-MS). <sup>1</sup>H NMR measurements were performed on either a  
30 Varian Mercury 300 or a Varian Inova 500, operating at <sup>1</sup>H frequencies of 300 and 500 MHz respectively. Chemical shifts are given in ppm with CDCl<sub>3</sub> as internal standard.

Purification was performed on a semipreparative HPLC with a mass triggered fraction collector, Shimadzu QP 8000 single quadrupole mass spectrometer equipped with 19 x 100 mm C8 column. The mobile phase used was, if nothing else is stated, acetonitrile and buffer (0.1 M NH<sub>4</sub>Ac:acetonitrile 95:5).

5 For isolation of isomers, a Kromasil CN E9344 (250 x 20 mm i.d.) column was used. Heptane:ethyl acetate:DEA 95:5:0.1 was used as mobile phase (1 ml/min). Fraction collection was guided using a UV-detector (330 nm).

#### 10 Synthesis of intermediates

The following intermediates were not commercially available and therefore prepared as described in Preparation A, (Chem. Ber., 100, 1967, p. 555).

#### Preparation A

##### 15 (a) 5,6-diphenyl-pyrazine-2-carboxylic acid

The monohydrochloride of 2,3-diaminopropionic acid (500 mg, 3.56 mmol) and benzil (890 mg, 4.23 mmol) were added to a solution of sodium hydroxide (677 mg, 16.93 mmol) in methanol (10 ml). An extra portion of methanol was added (5 ml) and the reaction mixture was refluxed for 20 minutes. The mixture was cooled to 25°C and air was bubbled  
20 through for 30 minutes. Hydrochloric acid (aq, 2 M) was added until the reaction mixture reached pH 2. The solution was extracted with diethyl ether. The combined diethyl ether phases were dried (MgSO<sub>4</sub>), filtrated and evaporated under reduced pressure to give the crude product. MS *m/z* 277 (M+H)<sup>+</sup>. The crude product was used in steps described below without further purification.

25

##### (b) 5,6-Bis-(4-bromophenyl)-pyrazine-2-carboxylic acid

The title compound was prepared essentially as described in Preparation A step (a), using monohydrochloride of 2,3-diaminopropionic acid (600 mg, 4.26 mmol) and 4,4'-  
30 dibromobenzil (1.745 g, 4.26 mmol, 90 %) as starting materials. The reaction mixture was refluxed for 2 hours and air was bubbled through for 1 hour. Hydrochloric acid (aq, 2 M)



was added until pH 2. The mixture was evaporated under reduced pressure and the residue was dissolved in water. The solution was extracted with diethyl ether, the combined diethyl ether phases were dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The crude product (500 mg, 27%) was used in steps described below without further purification. MS *m/z* 435, 437, 439 (M+H)<sup>+</sup>.

(c) 5,6-Di-*p*-tolyl-pyrazine-2-carboxylic acid

The title compound was prepared as described in Preparation A step (a) using 4,4'-dimethylbenzil (848 mg, 3.56 mmol). The reaction mixture was however refluxed for 1 hour and air was bubbled through the reaction mixture for about 7 hours. The mixture was evaporated and the residue was dissolved in water. Hydrochloric acid (aq, 2 M) was added until pH 2 was reached. The solution was extracted with diethyl ether. The combined diethyl ether phases were dried (MgSO<sub>4</sub>), filtered and evaporated under reduced pressure. The crude product (918 mg, 85%) was used in steps described below without further purification. MS *m/z* 305 (M+H)<sup>+</sup>.

(d) 5,6-Bis-(4-methoxyphenyl)pyrazine-2-carboxylic acid

The title compound was prepared as described in Preparation A step (c) using 4,4'-dimethoxybenzil (961 mg, 3.56 mmol) as starting material. The reaction mixture was refluxed over night and air was bubbled through the mixture for 8 hours. The crude product (435 mg, 36%) was used in steps described below without further purification. MS *m/z* 335 (M+H)<sup>+</sup>

(e) 5,6-Bis-(4-chlorophenyl) pyrazine-2-carboxylic acid

The title compound was prepared as described in Preparation A step (c) using 4,4'-dichlorobenzil (993 mg, 3.56 mmol). Reflux for 1 hour gave directly the crude product (923 mg, 75%) that was used in steps described below without further purification. MS *m/z* 343, 345, 347 (M-H)<sup>-</sup>.

(f) 5,6-Bis-(2-chlorophenyl)pyrazine-2-carboxylic acid

The title compound was prepared as described in Preparation A step (c) using 2,2'-dichlorobenzil (993 mg, 3.56 mmol). The crude product (895 mg, 73%) was used in steps described below without further purification. MS  $m/z$  343, 345, 347 (M-H)<sup>-</sup>.

5 (h) 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)ethane-1,2-dione

2-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)ethanone (2.7 g, 9.01 mmol) was dissolved in 1,2-dichloroethane (25 ml) and freshly made PCC (3.89 g, 18.02 mmol), pyridine (1.43 g, 18.02 mmol) and molecular sieves were added. The reaction mixture was refluxed under inert atmosphere overnight. The solution was cooled to 25 °C, filtered through Silica and  
10 then solvent was evaporated under reduced pressure. The crude product (1.9 g, 66%) was used directly in the next step. <sup>1</sup>H NMR (500 MHz)  $\delta$  7.97 (d, 2H), 7.84 (d, 1H), 7.52 (d, 2H), 7.46 (s, 1H), 7.44 (d, 1H).

(i) 5-(4-Chlorophenyl)-6-(2,4-dichlorophenyl)pyrazine-2-carboxylic acid and

15 6-(4-chlorophenyl)-5-(2,4-dichlorophenyl)pyrazine-2-carboxylic acid

The title compounds were prepared as described in Preparation A step (a), using 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)ethane-1,2-dione (1.85 g; 5.90 mmol) from Preparation A step (g) and the monochloride of 2,3-diaminopropionic acid (0.61 g, 5.90 mmol) as starting materials. The mixture was refluxed for 30 minutes and then directly  
20 worked-up. The crude product was allowed to stand over night to aromatise. Flash chromatography (SiO<sub>2</sub>, DCM:methanol 10:1, 1% Acetic acid) gave the isomer mixture (0.2 g, 10%). MS  $m/z$  377, 379, 381 (M-H)<sup>-</sup>.

### Examples of the Invention

#### Example 1

##### N-(1-piperidinyl)- 5,6-diphenyl-2-pyrazinecarboxamide

5,6-Diphenyl-pyrazine-2-carboxylic acid (500 mg, 1.81 mmol) from Preparation A, step (a), was dissolved in DCM (4 ml) and DMF (150  $\mu$ l). DMAP (22 mg, 0.18 mmol) and 1-aminopiperidine (218 mg, 2.17 mmol) were added and the solution was cooled to 0 °C. A  
30 slurry of EDC (1.99 mmol, in 2mL DCM and 100  $\mu$ l DMF) was added dropwise. The

reaction mixture was stirred at 25 °C. After 17 hours additional 1-aminopiperidine (40 mg, 0.40 mmol) and EDC (76 mg, 0.40 mmol) was added, and the mixture was stirred for an additional 3 hours. The crude was diluted with DCM (5ml) and washed with a saturated solution of NaHCO<sub>3</sub>. The organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated. Flash chromatography (SiO<sub>2</sub>, ethyl acetate:hexane 2:1) gave the subtitle compound (160 mg, 25%) as a white solid.

<sup>1</sup>H NMR (300 MHz) δ 9.41 (s, 1H), 8.52 (s, 1H), 7.50-7.29 (m, 10H), 2.94 (t, 4H), 1.81 (m, 4H), 1.50 (m, 2H).

MS *m/z* 359 (M+H)<sup>+</sup>.

### Example 2

#### *N*-(1-piperidinyl)- 5,6-bis(4-bromophenyl)-2-pyrazinecarboxamide

To 5,6-Bis-(4-bromophenyl)-pyrazine-2-carboxylic acid (108 mg, 0.25 mmol) from Preparation A, step (b), DMAP (0.025 mmol, in 500 µl DCM), 1-aminopiperidine (0.25 mmol, in 1100 µl DCM), EDC (0.27 mmol, in 1100 µl DCM and cooled to 8 °C) were added. The reaction mixture was stirred at 25 °C for 20 h, then washed with saturated NaHCO<sub>3</sub> solution, dried (MgSO<sub>4</sub>), filtered and evaporated. Semipreparatory HPLC (0.01% TEA in the buffered phase) gave the subtitle compound (6.7 mg, 5.4%).

<sup>1</sup>H NMR (300 MHz) δ 9.41 (s, 1H), 8.48 (s, 1H), 7.54 (d, 2H), 7.51 (d, 2H), 7.36 (d, 2H), 7.34 (d, 2H), 2.94 (t, 4H), 1.81 (m, 4H), 1.55-1.45 (m, 2H).

MS *m/z* 515, 517, 519 (M+H)<sup>+</sup>.

### Example 3

#### *N*-(1-piperidinyl)- 5,6-bis(4-methylphenyl)- 2-pyrazinecarboxamide

5,6-Di-*p*-tolyl-pyrazine-2-carboxylic acid (76 mg, 0.25 mmol) from Preparation A, step (c), was used as described in Example 2 to give the title compound (27 mg, 28%).

<sup>1</sup>H NMR (300 MHz) δ 9.35 (s, 1H), 8.57 (s, 1H), 7.38 (d, 4H), 7.18 (d, 2H), 7.13 (d, 2H), 2.92 (t, 4H), 2.40 (s, 3H), 2.37 (s, 3H), 1.86-1.75 (m, 4H), 1.54-1.44 (m, 2H).

MS *m/z* 387 (M+H)<sup>+</sup>.

Example 4N-(1-piperidinyl)- 5,6-bis(4-methoxyphenyl)- 2-pyrazinecarboxamide

5,6-Bis-(4-methoxyphenyl)-pyrazine-2-carboxylic acid (84 mg, 0.25 mmol) from Preparation A, step (d), was used as described Example 2 to give the title compound (20 mg, 19%).

<sup>1</sup>H NMR (300 MHz) δ 9.31 (s, 1H), 8.57 (s, 1H), 7.46 (d, 2H), 7.44 (d, 2H), 6.90 (d, 2H), 6.86 (d, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.93 (t, 4H), 1.80 (m, 4H), 1.54-1.45 (m, 2H).

MS *m/z* 419 (M+H)<sup>+</sup>.

Example 5N-(1-piperidinyl)- 5,6-bis(4-chlorophenyl)- 2-pyrazinecarboxamide

5,6-Bis-(4-chlorophenyl)-pyrazine-2-carboxylic acid (86 mg, 0.25 mmol) from Preparation A, step (e), was used as described in Example 2 to give the subtitle compound (16 mg, 15%).

<sup>1</sup>H NMR (300 MHz) δ 9.40 (s, 1H), 8.49 (s, 1H), 7.45-7.31 (m, 8H), 2.94 (t, 4H), 1.80 (m, 4H), 1.54-1.45 (m, 2H).

MS *m/z* 427, 429, 431 (M+H)<sup>+</sup>.

Example 6N-(1-piperidinyl)- 5,6-bis(2-chlorophenyl)- 2-pyrazinecarboxamide

5,6-Bis-(2-chlorophenyl)-pyrazine-2-carboxylic acid (86 mg, 0.25 mmol) from Preparation A, step (f), was used as described in Example 2 to give the subtitle compound (6 mg, 6%).

<sup>1</sup>H NMR (300 MHz) δ 9.52 (s, 1H), 8.52 (s, 1H), 7.44-7.17 (d, 8H), 2.94-2.88 (t, 4H), 1.85-1.70 (m, 4H), 1.52-1.44 (m, 2H).

MS *m/z* 427, 429, 431 (M+H)<sup>+</sup>.

Example 7N-cyclohexyl-5,6-diphenyl-2-pyrazinecarboxamide

5,6-diphenyl-pyrazine-2-carboxylic acid (70 mg, 0.25 mmol) from Preparation A, step (a), was reacted essentially as described in Example 2 but with cyclohexylamine (0.25 mmol,

in 1 ml DCM), DMAP (0.025 mmol, in 0.5 ml DCM), EDC (0.28 mmol, in 1 ml DCM, and cooled to 8 °C) and DMF (100 µl). Semipreparatory HPLC (0.15% TFA/water:acetonitrile 95:5 instead of the buffer phase) gave the title compound (7 mg, 8%) after washing with Na<sub>2</sub>CO<sub>3</sub> solution.

<sup>1</sup>H NMR (300 MHz) δ 9.41 (s, 1H), 7.78 (d, 1H), 7.49-7.28 (m, 10H), 4.12-3.97 (m, 1H), 2.13-1.23 (m, 10H).

MS *m/z* 358 (M+H)<sup>+</sup>.

#### Example 8

##### *N*-cyclohexyl-5,6-bis(4-bromophenyl)-2-pyrazinecarboxamide

5,6-Bis-(4-bromophenyl)-pyrazine-2-carboxylic acid (109 mg, 0.25 mmol) from Preparation A, step (b), was used as described in Example 7. Semipreparatory HPLC (0.15 % TFA/water:acetonitrile 95:5 instead of the buffer phase) gave the title compound (7 mg, 8%) after washing with Na<sub>2</sub>CO<sub>3</sub> solution.

<sup>1</sup>H NMR (300 MHz) δ 9.41 (s, 1H), 7.68 (s, 1H), 7.54 (d, 2H), 7.50 (d, 2H), 7.36 (d, 2H), 7.34 (d, 2H), 4.11-3.96(m, 1H), 2.12-1.20 (m, 10H).

MS *m/z* 514, 516, 518 (M+H)<sup>+</sup>.

#### Example 9

##### *N*-cyclohexyl-5,6-bis(4-methylphenyl)-2-pyrazinecarboxamide

5,6-Di-*p*-tolyl-pyrazine-2-carboxylic acid (76 mg, 0.25 mmol) from Preparation A, step (c), was used as described in Example 7. Semipreparatory HPLC (0.01% TEA in the buffer phase) gave the subtitle compound (4 mg, 4%).

<sup>1</sup>H NMR (300 MHz) δ 9.36 (s, 1H), 7.77 (d, 1H), 7.39 (d, 4H), 7.18 (d, 2H), 7.13 (d, 2H), 4.10-3.96 (m, 1H), 2.40 (s, 3H), 2.37 (s, 3H), 2.09-1.20 (m, 10H).

MS *m/z* 386 (M+H)<sup>+</sup>.

Example 10N-cyclohexyl-5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxamide

5,6-Bis-(4-methoxyphenyl)-pyrazine-2-carboxylic acid (76 mg, 0.25 mmol) from Preparation A, step (d), was used essentially as described in Example 7 but the reaction mixture was first stirred overnight, then more cyclohexylamine (25 mg, 0.25 mmol) was added and the mixture was stirred for an additional two days prior to workup.

Semipreparatory HPLC (0.15 % TFA in the buffered phase) gave the title compound (12 mg, 11%).

<sup>1</sup>H NMR (300 MHz) δ 9.32 (s, 1H), 7.76 (d, 1H), 7.47 (d, 2H), 7.45 (d, 2H), 6.90 (d, 2H), 6.86 (d, 2H), 4.10-3.96 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.09-1.17 (m, 10H).

MS *m/z* 418 (M+H)<sup>+</sup>.

Example 11N-cyclohexyl-5,6-bis(4-chlorophenyl)-2-pyrazinecarboxamide

5,6-Bis-(4-chlorophenyl)pyrazine-2-carboxylic acid (86 mg, 0.25 mmol) from Preparation A, step (e), was used as described in Example 10 to give the title compound (7 mg, 8%) after washing with Na<sub>2</sub>CO<sub>3</sub> solution.

<sup>1</sup>H NMR (300 MHz) δ 9.41 (s, 1H), 7.69 (s, 1H), 7.47-7.30 (m, 8H), 4.10-3.97 (m, 1H), 2.10-1.18 (m, 10H).

MS *m/z* 426, 428, 430 (M+H)<sup>+</sup>.

Example 12N-cyclohexyl-5,6-bis(2-chlorophenyl)-2-pyrazinecarboxamide

5,6-Bis-(2-chlorophenyl)-pyrazine-2-carboxylic acid (86 mg, 0.25 mmol) from preparation A step (f) was used as described in Example 10, to give the title compound (14 mg, 13%).

<sup>1</sup>H NMR (300 MHz) δ 9.51 (s, 1H), 7.74 (s, 1H), 7.41-7.18 (m, 8H), 4.10-3.97 (m, 1H), 2.07-1.14 (m, 10H).

MS *m/z* 426, 428, 430 (M+H)<sup>+</sup>.

Example 13N,5,6-triphenyl-2-pyrazinecarboxamide

To 5,6-Diphenyl-pyrazine-2-carboxylic acid (70 mg, 0.25 mmol) from Preparation A, step (a), DMAP (0.025 mmol, in 0.5 ml DCM), aniline (0.25 mmol, in 1 ml DCM), EDC (0.28 mmol, in 1ml DCM, cooled to 8 °C) and DMF (100 µl) were added. The reaction mixture was stirred at 25 °C over night, then worked up as described in Example 2.

Semipreparatory HPLC (0.15 % TFA/water:acetonitrile 95:5 instead of the buffer phase) gave the title compound (27 mg, 30%) after washing with Na<sub>2</sub>CO<sub>3</sub> solution.

<sup>1</sup>H NMR (300 MHz) δ 9.75 (s, 1H), 9.52 (d, 1H), 7.80 (d, 2H), 7.55-7.32 (m, 12H), 7.20 (t, 1H).

MS *m/z* 352 (M+H)<sup>+</sup>.

Example 14N-phenyl-5,6-bis(4-methylphenyl)-2-pyrazinecarboxamide

5,6-Di-*p*-tolyl-pyrazine-2-carboxylic acid (77 mg, 0.25 mmol) from Preparation A, step (c), was used as described in Example 13 to give the subtitle compound (28 mg, 29%).

<sup>1</sup>H NMR (500 MHz) δ 9.78 (s, 1H), 9.49 (s, 1H), 7.81 (d, 2H), 7.47-7.43 (m, 6H), 7.25-7.17 (m, 5H), 2.45 (s, 3H), 2.41 (s, 3H).

MS *m/z* 380 (M+H)<sup>+</sup>.

Example 15N-phenyl-5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxamide

5,6-Bis-(4-methoxyphenyl)-pyrazine-2-carboxylic acid (85 mg, 0.25 mmol) from Preparation A step (d), was used as described in Example 13, to give the title compound (33 mg, 32%).

<sup>1</sup>H NMR (300 MHz) δ 9.74 (s, 1H), 9.42 (s, 1H), 7.79 (d, 2H), 7.50 (d, 4H), 7.42 (t, 2H), 7.19 (t, 1H), 6.94 (d, 2H), 6.89 (d, 2H), 3.88 (s, 3H), 3.85 (s, 3H).

MS *m/z* 412 (M+H)<sup>+</sup>.

Example 16N-phenyl-5,6-bis(4-chlorophenyl)-2-pyrazinecarboxamide

5,6-Bis-(4-chlorophenyl)-pyrazine-2-carboxylic acid (87 mg, 0.25 mmol) from Preparation A, step (e), was used as described in Example 13, to give the subtitle compound (6 mg, 6%).

<sup>1</sup>H NMR (300 MHz) δ 9.66 (s, 1H), 9.52 (s, 1H), 7.79 (d, 2H), 7.48-7.35 (m, 10H), 7.21 (t, 1H).

MS *m/z* 420, 422, 424 (M+H)<sup>+</sup>.

Example 17N-phenyl-5,6-bis(2-chlorophenyl)-2-pyrazinecarboxamide

5,6-Bis-(2-chloro-phenyl)-pyrazine-2-carboxylic acid (87 mg, 0.25 mmol) from Preparation A, step (f), was treated as described in Example 13, to give the title compound (27 mg, 25%).

<sup>1</sup>H NMR (500 MHz) δ 9.73 (s, 1H), 9.66 (s, 1H), 7.81(d, 2H), 7.46-7.22 (m, 11H).

MS *m/z* 420, 422, 424 (M+H)<sup>+</sup>.

Example 185-(4-Chlorophenyl)-6-(2,4-dichlorophenyl)pyrazine-2-carboxylic acid piperidin-1-ylamide and 6-(4-chlorophenyl)-5-(2,4-dichlorophenyl)pyrazine-2-carboxylic acid piperidin-1-ylamide

The mixture of 5-(4-chlorophenyl)-6-(2,4-dichlorophenyl)pyrazine-2-carboxylic acid and 6-(4-chlorophenyl)-5-(2,4-dichlorophenyl)pyrazine-2-carboxylic acid (78 mg, 0.205 mmol) from Preparation A step (i) and thionyl chloride (147 mg, 1.23 mmol) were refluxed in toluene (2ml) for 3 hours. The solvent and reagents were evaporated under reduced pressure and the intermediates were dissolved in DCM (1 ml). TEA (42 mg, 0.41 mmol) and 1-aminopiperidine (21 mg, 0.205 mmol) were dissolved in DCM (1ml) and added. The reaction mixture was stirred at 25 °C overnight and then evaporated under reduced pressure. Flash chromatography (SiO<sub>2</sub>, heptane:ethyl acetate 1:1) gave a mixture of the title compounds (45 mg, 47%, ratio of isomers 0.5:1). <sup>1</sup>H NMR (300 MHz) δ 9.46 (s, 1H), 8.39 (s, 1H), 7.47-7.28 (m, 7H), 3.02-2.84 (m, 4H), 1.89-1.73 (m, 4H), 1.57-1.41 (m, 2H) and



9.42 (s, 1H), 8.51 (s, 1H), 7.47-7.28 (m, 7H), 3.02-2.84 (m, 4H), 1.89-1.73 (m, 4H), 1.57-1.41 (m, 2H).

#### Example 18 (a)

5 *N*-(1-piperidinyl)- 5-(4-chlorophenyl)-6-(2,4-dichlorophenyl)-2-pyrazinecarboxamide

The title compound was isolated from the mixture prepared in Example 18 (35 mg) by preparative chromatography (9 mg, 26%). <sup>1</sup>H NMR (300 MHz) δ 9.46 (s, 1H), 8.38 (s, 1H), 7.46-7.24 (m, 7H), 2.89 (t, 4H), 1.78 (p, 4H), 1.52-1.40 (m, 2H).

10 Example 18 (b)

*N*-(1-piperidinyl)- 6-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-pyrazinecarboxamide

The title compound was isolated from the mixture prepared in Example 18 (35 mg) by preparative chromatography (11 mg, 31%). <sup>1</sup>H NMR (300 MHz) δ 9.42 (s, 1H), 8.50 (s, 1H), 7.39-7.30 (m, 7H), 2.93 (t, 4H), 1.80 (p, 4H), 1.54-1.43 (m, 2H).

15

#### Pharmacological Activity

Compounds of the present invention are active against the receptor product of the CB1 gene. The affinity of the compounds of the invention for central cannabinoid receptors is demonstrable in methods described in Devane et al , Molecular Pharmacology, 1988, 34,605 or those described in WO01/70700 or EP 656354. Alternatively the assay may be performed as follows.

20

10μg of membranes prepared from cells stably transfected with the CB1 gene were suspended in 200μl of 100mM NaCl, 5mM MgCl<sub>2</sub>, 1mM EDTA, 50mM HEPES (pH 7.4), 1mM DTT, 0.1% BSA and 100μM GDP. To this was added an EC80 concentration of agonist (CP55940), the required concentration of test compound and 0.1μCi [<sup>35</sup>S]-GTPγS. The reaction was allowed to proceed at 30°C for 45 min. Samples were then transferred on to GF/B filters using a cell harvester and washed with wash buffer (50mM Tris (pH 7.4), 5mM MgCl<sub>2</sub>, 50mM NaCl). Filters were then covered with scintillant and counted for the amount of [<sup>35</sup>S]-GTPγS retained by the filter.

25

30

Activity is measured in the absence of all ligands (minimum activity) or in the presence of an EC80 concentration of CP55940 (maximum activity). These activities are set as 0% and 100% activity respectively. At various concentrations of novel ligand, activity is

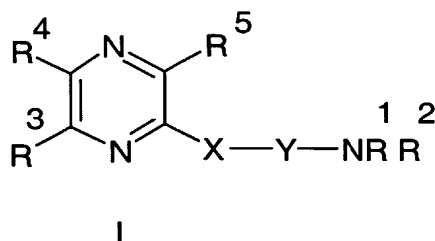
calculated as a percentage of the maximum activity and plotted. The data are fitted using the equation  $y=A+((B-A)/(1+((C/x)^D)))$  and the IC<sub>50</sub> value determined as the concentration required to give half maximal inhibition of GTPγS binding under the conditions used.

5

The compounds of the present invention are active at the CB1 receptor (IC<sub>50</sub> <1 micromolar). Most preferred compounds have IC<sub>50</sub> <200 nanomolar.

Claims

1. A compound of formula (I)



and pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, in which

R<sup>1</sup> and R<sup>2</sup> independently represent :

a C<sub>1-6</sub>alkyl group;

an (amino)C<sub>1-4</sub>alkyl- group in which the amino is optionally substituted by one or more C<sub>1-3</sub>alkyl groups;

an optionally substituted non-aromatic C<sub>3-15</sub>carbocyclic group;

a (C<sub>3-12</sub>cycloalkyl)C<sub>1-3</sub>alkyl- group;

a group -(CH<sub>2</sub>)<sub>r</sub>(phenyl)<sub>s</sub> in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2

and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more C<sub>1-3</sub>alkyl groups, hydroxy or benzyl ;

1-adamantylmethyl;

a group -(CH<sub>2</sub>)<sub>t</sub> Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more C<sub>1-3</sub>alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a C<sub>1-5</sub>alkyl group, a C<sub>1-5</sub>alkoxy group or halo;

or R<sup>1</sup> represents H and R<sup>2</sup> is as defined above;

or  $R^1$  and  $R^2$  together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more  $C_{1-3}$ alkyl groups, hydroxy or benzyl ;

X is CO or  $SO_2$  ;

Y is absent or represents NH optionally substituted by a  $C_{1-3}$ alkyl group;

$R^3$  and  $R^4$  independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one , two or three groups represented by Z;

Z represents a  $C_{1-3}$ alkyl group, a  $C_{1-3}$ alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di  $C_{1-3}$ alkylamino, mono or di  $C_{1-3}$ alkylamido,  $C_{1-3}$ alkylsulphonyl,  $C_{1-3}$ alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di  $C_{1-3}$ alkyl carbamoyl, sulphamoyl and acetyl; and

$R^5$  is H, a  $C_{1-3}$ alkyl group, a  $C_{1-3}$ alkoxymethyl group, trifluoromethyl, a hydroxy $C_{1-3}$ alkyl group,  $C_{1-3}$ alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di  $C_{1-3}$ alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula  $-CONHNR^aR^b$  wherein  $R^a$  and  $R^b$  are as previously defined for  $R^1$  and  $R^2$  respectively and;

with the proviso that when  $R^1$  and  $R^2$  together with the nitrogen atom to which they are attached represent 4-methylpiperazin-1-yl or  $R^1$  represents H and  $R^2$  represents methyl or 1-benzylpiperidin-4-yl; X is CO; Y is absent and  $R^5$  is H; then  $R^3$  and  $R^4$  do not both represent 4-methoxyphenyl.

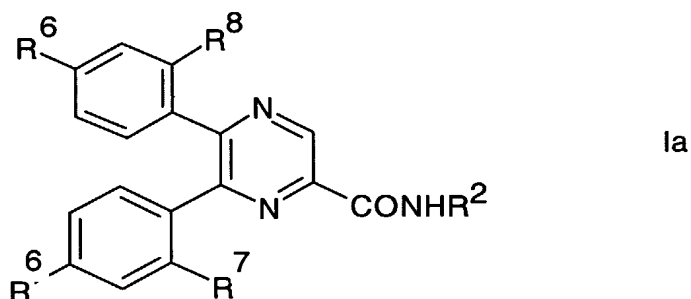
2. A compound according to claim 1 in which  $R^1$  represents H,  $R^2$  represents cyclohexyl, X is CO and Y is absent.

3. A compound according to claim 1 in which  $R^1$  and  $R^2$  together with the nitrogen atom to which they are attached represent 1-piperidinyl.

4. A compound according to claim 1 in which  $R^1$  represents H and  $R^2$  represents phenyl.

5

5. A compound according to claim 1 as represented by formula Ia



and pharmaceutically acceptable salts, solvates and crystalline forms thereof, in which

- 10  $R^2$  represents cyclohexyl, 1-piperidinyl or phenyl ;  
 $R^6$  represents H, chloro, bromo, methyl or methoxy; and  
 when  $R^7$  represents H,  $R^8$  represents H or chloro; and  
 when  $R^7$  represents chloro,  $R^8$  represents H or chloro.

15 6. A compound according to any one of claims 1 to 4 in which  $R^5$  is H.

7. A compound according to any one of claims 1 to 4 in which X is CO.

8. A compound according to any one of claims 1 to 4 in which X is SO<sub>2</sub>.

20

9. A compound according to any one of claims 1 to 4 in which Y is absent.

10. A compound selected from:

*N*-(1-piperidinyl)- 5,6-diphenyl-2-pyrazinecarboxamide;

25 *N*-(1-piperidinyl)- 5,6-bis(4-bromophenyl)-2-pyrazinecarboxamide;

*N*-(1-piperidiny)- 5,6-bis(4-methylphenyl)- 2-pyrazinecarboxamide;  
*N*-(1-piperidiny)- 5,6-bis(4-methoxyphenyl)- 2-pyrazinecarboxamide;  
*N*-(1-piperidiny)- 5,6-bis(4-chlorophenyl)- 2-pyrazinecarboxamide;  
*N*-(1-piperidiny)- 5,6-bis(2-chlorophenyl)- 2-pyrazinecarboxamide;  
5 *N*-cyclohexyl-5,6-diphenyl-2-pyrazinecarboxamide;  
*N*-cyclohexyl-5,6-bis(4-bromophenyl)-2-pyrazinecarboxamide;  
*N*-cyclohexyl-5,6-bis(4-methylphenyl)-2-pyrazinecarboxamide;  
*N*-cyclohexyl-5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxamide;  
*N*-cyclohexyl-5,6-bis(4-chlorophenyl)- 2-pyrazinecarboxamide;  
10 *N*-cyclohexyl-5,6-bis(2-chlorophenyl)-2-pyrazinecarboxamide;  
*N*,5,6-triphenyl-2-pyrazinecarboxamide;  
*N*-phenyl-5,6-bis(4-methylphenyl)-2-pyrazinecarboxamide;  
*N*-phenyl-5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxamide;  
*N*-phenyl-5,6-bis(4-chlorophenyl)-2-pyrazinecarboxamide;  
15 *N*-phenyl-5,6-bis(2-chlorophenyl)-2-pyrazinecarboxamide;  
*N*-(1-piperidiny)- 5-(4-chlorophenyl)-6-(2,4-dichlorophenyl)-2-pyrazinecarboxamide; and  
*N*-(1-piperidiny)- 6-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-pyrazinecarboxamide;  
and where applicable, optical isomers, tautomers, stereoisomers and racemates thereof as  
well as pharmaceutically acceptable salts, solvates and crystalline forms thereof.

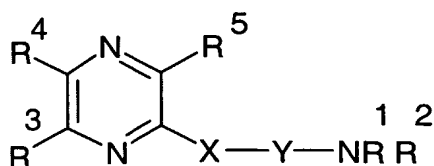
20

11. A compound of formula I as claimed in any previous claim for use as a medicament.

12. A pharmaceutical formulation comprising a compound of formula I, as defined in any  
one of claims 1 to 10 and a pharmaceutically acceptable adjuvant, diluent or carrier.

25

13. Use of a compound of formula I



and pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, in which

$R^1$  and  $R^2$  independently represent :

- 5 a  $C_{1-6}$ alkyl group;
- an (amino) $C_{1-4}$ alkyl- group in which the amino is optionally substituted by one or more  $C_{1-3}$ alkyl groups;
- an optionally substituted non-aromatic  $C_{3-15}$ carbocyclic group;
- a  $(C_{3-12}$ cycloalkyl) $C_{1-3}$ alkyl- group;
- 10 a group  $-(CH_2)_r(phenyl)_s$  in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2 and the phenyl groups are optionally independently substituted by one, two or three groups represented by Z;
- naphthyl;
- anthracenyl;
- 15 a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic group is optionally substituted by one or more  $C_{1-3}$ alkyl groups, hydroxy or benzyl ;
- 1-adamantylmethyl;
- a group  $-(CH_2)_t$  Het in which t is 0,1, 2, 3 or 4, and the alkylene chain is optionally
- 20 substituted by one or more  $C_{1-3}$ alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a  $C_{1-5}$ alkyl group, a  $C_{1-5}$ alkoxy group or halo;
- or  $R^1$  represents H and  $R^2$  is as defined above;
- or  $R^1$  and  $R^2$  together with the nitrogen atom to which they are attached represent a
- 25 saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one

of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more C<sub>1-3</sub>alkyl groups, hydroxy or benzyl ;

X is CO or SO<sub>2</sub> ;

Y is absent or represents NH optionally substituted by a C<sub>1-3</sub>alkyl group;

R<sup>3</sup> and R<sup>4</sup> independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one , two or three groups represented by Z;

Z represents a C<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di C<sub>1-3</sub>alkylamino, mono or di C<sub>1-3</sub>alkylamido, C<sub>1-3</sub>alkylsulphonyl, C<sub>1-3</sub>alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C<sub>1-3</sub>alkyl carbamoyl, sulphamoyl and acetyl; and

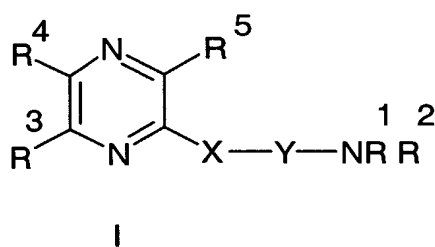
R<sup>5</sup> is H, a C<sub>1-3</sub>alkyl group, a C<sub>1-3</sub>alkoxymethyl group, trifluoromethyl, a hydroxyC<sub>1-3</sub>alkyl group, C<sub>1-3</sub>alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C<sub>1-3</sub>alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula -CONHNR<sup>a</sup>R<sup>b</sup> wherein R<sup>a</sup> and R<sup>b</sup> are as previously defined for R<sup>1</sup> and R<sup>2</sup> respectively;

in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems, and extended abuse, addiction and/or relapse indications.

14. A method of treating obesity, psychiatric disorders, psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders,



memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, neurological disorders, neurological disorders , Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal system, and extended abuse, addiction and/or relapse indications, comprising administering a pharmacologically effective amount of a compound of formula I



and pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, in which

$R^1$  and  $R^2$  independently represent :

a  $C_{1-6}$ alkyl group;

an (amino) $C_{1-4}$ alkyl- group in which the amino is optionally substituted by one or more

$C_{1-3}$ alkyl groups;

an optionally substituted non-aromatic  $C_{3-15}$ carbocyclic group;

a ( $C_{3-12}$ cycloalkyl) $C_{1-3}$ alkyl- group;

a group  $-(CH_2)_r(phenyl)_s$  in which r is 0,1, 2, 3 or 4, s is 1 when r is 0 otherwise s is 1 or 2

and the phenyl groups are optionally independently substituted by one, two or three groups

represented by Z;

naphthyl;

anthracenyl;

a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen wherein the heterocyclic

group is optionally substituted by one or more  $C_{1-3}$ alkyl groups, hydroxy or benzyl ;

1-adamantylmethyl;

a group  $-(CH_2)_t$  Het in which t is 0, 1, 2, 3 or 4, and the alkylene chain is optionally substituted by one or more  $C_{1-3}$ alkyl groups and Het represents an aromatic heterocycle optionally substituted by one, two or three groups selected from a  $C_{1-5}$ alkyl group, a  $C_{1-5}$ alkoxy group or halo;

or  $R^1$  represents H and  $R^2$  is as defined above;

or  $R^1$  and  $R^2$  together with the nitrogen atom to which they are attached represent a saturated 5 to 8 membered heterocyclic group containing one nitrogen and optionally one of the following : oxygen, sulphur or an additional nitrogen; wherein the heterocyclic group is optionally substituted by one or more  $C_{1-3}$ alkyl groups, hydroxy or benzyl ;

X is CO or  $SO_2$  ;

Y is absent or represents NH optionally substituted by a  $C_{1-3}$ alkyl group;

$R^3$  and  $R^4$  independently represent phenyl, thienyl or pyridyl each of which is optionally substituted by one , two or three groups represented by Z;

Z represents a  $C_{1-3}$ alkyl group, a  $C_{1-3}$ alkoxy group, hydroxy, halo, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, trifluoromethylsulphonyl, nitro, amino, mono or di  $C_{1-3}$ alkylamino, mono or di  $C_{1-3}$ alkylamido,  $C_{1-3}$ alkylsulphonyl,  $C_{1-3}$ alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di  $C_{1-3}$ alkyl carbamoyl, sulphamoyl and acetyl; and

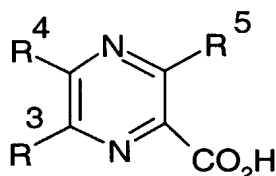
$R^5$  is H, a  $C_{1-3}$ alkyl group, a  $C_{1-3}$ alkoxymethyl group, trifluoromethyl, a hydroxy $C_{1-3}$ alkyl group,  $C_{1-3}$ alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di  $C_{1-3}$ alkylcarbamoyl, acetyl, or hydrazinocarbonyl of formula  $-CONHNR^aR^b$  wherein  $R^a$  and  $R^b$  are as previously defined for  $R^1$  and  $R^2$  respectively;

to a patient in need thereof.

15. A compound as defined in any one of claims 1 to 10 for use in the treatment of obesity.

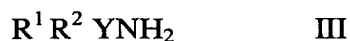
16. A process for the preparation of a compound of formula I comprising

a) reacting a compound of formula II



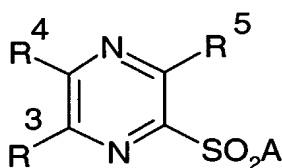
II

5 in which  $R^3$ ,  $R^4$  and  $R^5$  are as previously defined with an amine of formula III



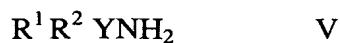
10 in an inert solvent in the presence of a coupling agent and optionally in the presence of a catalyst at a temperature in the range of  $-25^\circ\text{C}$  to  $150^\circ\text{C}$  to give a compound of formula I in which X is CO; or

b) reacting a compound of formula IV



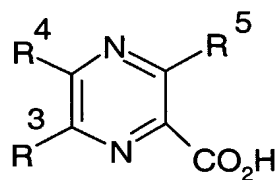
IV

15 in which  $R^3$ ,  $R^4$  and  $R^5$  are as previously defined and A represents halo with an amine of formula V



20 in an inert solvent and optionally in the presence of a catalyst at a temperature in the range of  $-25^\circ\text{C}$  to  $150^\circ\text{C}$  to give a compound of formula I in which X is  $\text{SO}_2$ .

17. A compound of formula II



II

- 5 in which R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as previously defined with the exception of 5,6-diphenyl-2-pyrazinecarboxylic acid and 5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxylic acid.

# INTERNATIONAL SEARCH REPORT

Inter ☐ National Application No  
PCT/GB 02/05742

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D241/24 A61K31/495 A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CH 458 361 A (EPROVA AG) 30 June 1968 (1968-06-30) cited in the application claims; examples ---	17
A	WO 92 02513 A (FUJISAWA PHARMACEUTICAL CO) 20 February 1992 (1992-02-20) cited in the application claim 1; examples 26-29,31-33 ---	1-12
A	EP 0 656 354 A (SANOFI SA) 7 June 1995 (1995-06-07) cited in the application claims --- -/--	1-16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

7 April 2003

Date of mailing of the international search report

15/04/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Menegaki, F

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 02/05742

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>HOWLETT A C ET AL: "AZIDO- AND ISOTHIOCYANATO-SUBSTITUTED ARYL PYRAZOLES BIND COVALENTLY TO THE CB1 CANNABINOID RECEPTOR AND IMPAIR SIGNAL TRANSDUCTION" JOURNAL OF NEUROCHEMISTRY, NEW YORK, NY, US, vol. 74, no. 5, 2000, pages 2174-2181, XP001097394 ISSN: 0022-3042 figure 1</p>	1-16
A	<p>EP 0 397 859 A (TERUMO CORP) 22 November 1990 (1990-11-22) example 14; table 1</p>	17

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/GB 02/05742

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
CH 458361	A	30-06-1968	NONE	
WO 9202513	A	20-02-1992	WO 9202513 A1 JP 6501926 T	20-02-1992 03-03-1994
EP 0656354	A	07-06-1995	FR 2713224 A1 FR 2713225 A1 AT 154012 T AU 685518 B2 AU 7899994 A BR 1100984 A3 CA 2136893 A1 CN 1110968 A ,B CZ 9403016 A3 DE 69403614 D1 DE 69403614 T2 DK 656354 T3 EP 0656354 A1 ES 2105575 T3 FI 945690 A GR 3024470 T3 HK 1000599 A1 HU 71498 A2 IL 111719 A JP 3137222 B2 JP 7309841 A JP 2001026541 A NO 944625 A NZ 270025 A PL 306067 A1 RU 2141479 C1 SG 68570 A1 SI 656354 T1 US 5624941 A ZA 9409342 A	09-06-1995 09-06-1995 15-06-1997 22-01-1998 15-06-1995 14-03-2000 21-06-1995 01-11-1995 14-06-1995 10-07-1997 22-01-1998 29-12-1997 07-06-1995 16-10-1997 03-06-1995 28-11-1997 09-04-1998 28-11-1995 28-10-1999 19-02-2001 28-11-1995 30-01-2001 06-06-1995 26-09-1995 12-06-1995 20-11-1999 20-06-2000 31-10-1997 29-04-1997 09-10-1995
EP 0397859	A	22-11-1990	JP 1128971 A JP 1128972 A JP 1824748 C JP 5036435 B JP 1135775 A JP 1824749 C JP 5036434 B EP 0397859 A1 WO 8904308 A1	22-05-1989 22-05-1989 10-02-1994 31-05-1993 29-05-1989 10-02-1994 31-05-1993 22-11-1990 18-05-1989